UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Act of 1934

Date of Report (Date of earliest event reported):
October 20, 2021

TCR^2 THERAPEUTICS INC.
(Exact name of registrant as specified in its charter)

Delaware	**001-38811**	**47-4152751**
(State or other jurisdiction of incorporation or organization)	**(Commission File Number)**	**(I.R.S. Employer Identification Number)**

100 Binney Street, Suite 710 **Cambridge, Massachusetts** **(Address of principal executive offices)**	**02142** **(Zip Code)**

Registrant's telephone number, including area code: (617) 949-5200

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13d-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock	**TCRR**	**The Nasdaq Stock Market, LLC**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On October 20, 2021, TCR^2 Therapeutics Inc. (the "Company") issued a press release titled "TCR^2 Therapeutics Reviews Pipeline and Strategy at R&D Day." A copy of the press release is attached as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference.

The information under this Item 7.01, including Exhibit 99.1 attached hereto, is being furnished herewith and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such filing.

Item 8.01 Other Events.

The Company from time to time presents and/or distributes to the investment community slide presentations to provide updates and summaries of its business. On October 20, 2021, the Company hosted a virtual R&D Day with a conference call and webcast to discuss new programs and provide highlights from its emerging TRuC pipeline programs. A copy of its "Engaging the TCR to Transform the Treatment of Solid Tumors" slide presentation is being filed herewith as Exhibit 99.2 to this Current Report on Form 8-K and incorporated herein by reference. The Company undertakes no obligation to update, supplement or amend the materials attached hereto as Exhibit 99.2.

Statements contained under this Item 8.01, including Exhibit 99.2, regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Such statements include, but are not limited to: express or implied statements regarding TCR^2's expectations for the Phase 1/2 clinical trial of gavo-cel; TCR^2's expectations for the safety and efficacy of its product candidates and enhancements, including gavo-cel, TC-510 and TC-520, compared to current T-cell therapy approaches; TCR^2'sexpectations regarding the timing of determining an RP2D for gavo-cel, TCR^2's expectations regarding the timing of INDs, TCR^2's expectations regarding the estimated patient populations and related market opportunities in gavo-cel's, TC-510's and TC-520's targeted indications; TCR^2's expectations regarding manufacturing of its product candidates, and TCR^2's expectations regarding its product candidate pipeline and business development opportunities.

Any forward-looking statements are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. Risks that contribute to the uncertain nature of the forward-looking statements include, without limitation: uncertainties inherent in clinical studies and in the availability and timing of data from ongoing clinical studies; whether interim results from a clinical trial will be predictive of the final results of a trial; the possibility that positive results from preclinical studies and correlative studies may not necessarily be predictive of the results of TCR^2's planned clinical trials, including the Phase 1/2 clinical trial of gavo-cel; the risk that the results from the Phase 1/2 clinical trial of gavo-cel will not support further development and marketing approval; the risk that TCR^2 may be unable to gain approval of gavo-cel and its other product candidates on a timely basis, if at all; the risk that TCR^2 has over-estimated the potential patient population for its product candidates, if approved; the risk that the current COVID-19 pandemic will impact TCR^2's clinical trials and other operations; and other risks set forth under the caption "Risk Factors" in TCR^2's most recent Annual Report on Form 10-K, most recent Quarterly Report on Form 10-Q and its other filings with the Securities and Exchange Commission. All forward-looking statements contained in this presentation speak only as of the date on which they were made. The Company undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Press release issued by TCR^2 Therapeutics Inc. on October 20, 2021
99.2	Copy of TCR^2 Therapeutics Inc. slide presentation dated October 20, 2021
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

TCR^2 THERAPEUTICS INC.

By: /s/ Mayur (Ian) Somaiya

Name: Mayur (Ian) Somaiya

Title: Chief Financial Officer

Date: October 20, 2021

Exhibit 99.1

TCR^2 Therapeutics Reviews Pipeline and Strategy at R&D Day

- gavo-cel recommended Phase 2 dose (RP2D) identification before year-end

- Anticipated IND filing for TC-510 in 1Q22

- Identification of CD70-targeted lead candidate

- Anticipated allogeneic program lead candidate in 2022

- Expansion of platform into autoimmune diseases with TRuC Tregs

- TCR^2 to host a webcast on Wednesday, October 20 at 8:00a.m. ET

CAMBRIDGE, Mass., October 20, 2021 - TCR^2 Therapeutics Inc. (Nasdaq: TCRR), a clinical-stage cell therapy company with a pipeline of novel T cell therapies for patients suffering from solid tumors, today unveiled new programs and provided highlights from its emerging TRuC pipeline programs during its first virtual R&D Day.

“At TCR^2, our mission is to build the next great cell therapy company in solid tumors based on the early success of our mesothelin franchise and an emerging pipeline which will extend our reach into new cancer patient populations and beyond,” said Garry Menzel, Ph.D., President and Chief Executive Officer of TCR^2 Therapeutics. “Today we will review our narrowed focus on solid tumors and unveil new strategies to potentially further enhance the persistence and efficacy of our TRuC-T cells. In addition, we will introduce compelling preclinical data for our TRuC Tregs, which could expand our footprint into the autoimmune disease setting. We believe that TCR^2 is already helping to change the treatment paradigm for patients with treatment-refractory solid tumors and, through continued innovation, will progress our re-prioritized pipeline to patients with a variety of unmet medical needs.”

Pipeline Updates

Gavo-cel:

- TCR^2 announced today the completion of the 3-patient cohort at the new dose level 3.5A ($3x10^8/m^2$ following lymphodepletion) using a split dosing approach. Two patients were evaluable for safety. In both cases, gavo-cel was well-tolerated with no patients experiencing on-target, off tumors toxicities or Grade ≥3 cytokine release syndrome (CRS) non-hematologic toxicities.
- TCR^2 anticipates the identification of the RP2D in 4Q21.

TC-110:

- TCR^2 announced today that, in alignment with its pipeline prioritization on solid tumors, the Company has deprioritized the development of TC-110 for the treatment of patients with CD19+ non-Hodgkin lymphoma or adult acute lymphoblastic leukemia and plans instead to evaluate business development options.

TC-510:

- TCR^2 announced today the Company anticipates the IND filing for its first TRuC-T cell enhanced with a PD1xCD28 switch receptor to be in 1Q22.

TC-520:

- TCR^2 announced today the selection of its lead candidate targeting CD70 co-expressing an IL-15 enhancement as TC-520. In new preclinical data highlighted at the R&D Day, TC-520 enhanced with membrane-bound IL-15 resulted in a significant increase in TC-520 cells with a CD8+ naïve/T memory stem cells phenotyope, improved autonomous persistence as well as increased expansion following repeated stimulation with CD70-expressing cancer cell lines.
- The Company anticipates initiating IND-enabling studies for TC-520 with an indication focus on renal cell carcinoma in 2022.

Allogeneic:

- TCR^2 announced today new preclinical data demonstrating allogeneic (off-the-shelf) TRuC-T cells targeting mesothelin that utilized a CRISPR/Cas9 endonucleases approach and the use of fully human TCRγ/δ domains reduced the risk of immunogencity and host rejection, lacked alloreactivity while maintaining clearance of tumor cells comparable to autologous TRuC-T cells targeting mesothelin.
- TCR^2 is currently evaluating the combination of enhancements with allogeneic TRuC-T cells to potentially improve persistence.
- The Company anticipates the identification of a lead candidate for its allogeneic program in 2022.

TRuC Tregs:

- TCR^2 announced today new preclinical data demonstrating proof-of-concept for TRuC Treg cells targeting HLA-A*02 for the prevention of Graft versus Host Disease (GvHD). In *in vitro* and *in vivo* experiments, TRuC Tregs utilizing the full TCR signaling complex promoted and stabilized Tregs by suppressing the proliferation of mismatched effector cells and inhibiting the production of cytokines in a dose dependent manner.
- TCR^2 plans to evaluate business development options to enable the treatment of patients with GvHD and other autoimmune diseases.

About TCR^2 Therapeutics

TCR^2 Therapeutics Inc. is a clinical-stage cell therapy company developing a pipeline of novel T cell therapies for patients suffering from solid tumors. The company is focused on the discovery and development of product candidates against novel and complex targets utilizing its proprietary T cell receptor (TCR) Fusion Construct T cells (TRuC®-T cells). The TRuC platform is designed to specifically recognize and kill cancer cells by harnessing signaling from the entire TCR, independent of human leukocyte antigens (HLA). For more information about TCR^2, please visit www.tcr2.com.

TCR^2 Therapeutics Conference Call and Webcast

TCR^2 Therapeutics will host a conference call and webcast on Wednesday, October 20 at 8:00am E.T. In order to participate in the conference call, please dial 866-220-8062 (domestic) or 470-495-9169 (international) and refer to confirmation number 1597681. The webcast and presentation will be made available on the TCR^2 Therapeutics website in the Investors section under Events at investors.tcr2.com/events. Following the live audio webcast, a replay will be available on the Company's website for approximately 30 days.

Forward-looking Statements

This press release contains forward-looking statements and information within the meaning of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. The use of words such as "may," "will," "could", "should," "expects," "intends," "plans," "anticipates," "believes," "estimates," "predicts," "projects," "seeks," "endeavor," "potential," "continue" or the negative of such words or other similar expressions can be used to identify forward-looking statements. These forward-looking statements include, but are not limited to, express or implied statements regarding TCR^2's expectations for the Phase 1/2 clinical trial of gavo-cel; TCR^2's expectations for the safety and efficacy of its product candidates and enhancements, including gavo-cel, TC-510 and TC-520, compared to current T-cell therapy approaches; TCR^2's expectations regarding the timing of determining an RP2D for gavo-cel, TCR^2's expectations regarding the timing of INDs, and TCR^2's expectations regarding the estimated patient populations and related market opportunities in gavo-cel's, TC-510's and TC-520's targeted indications.

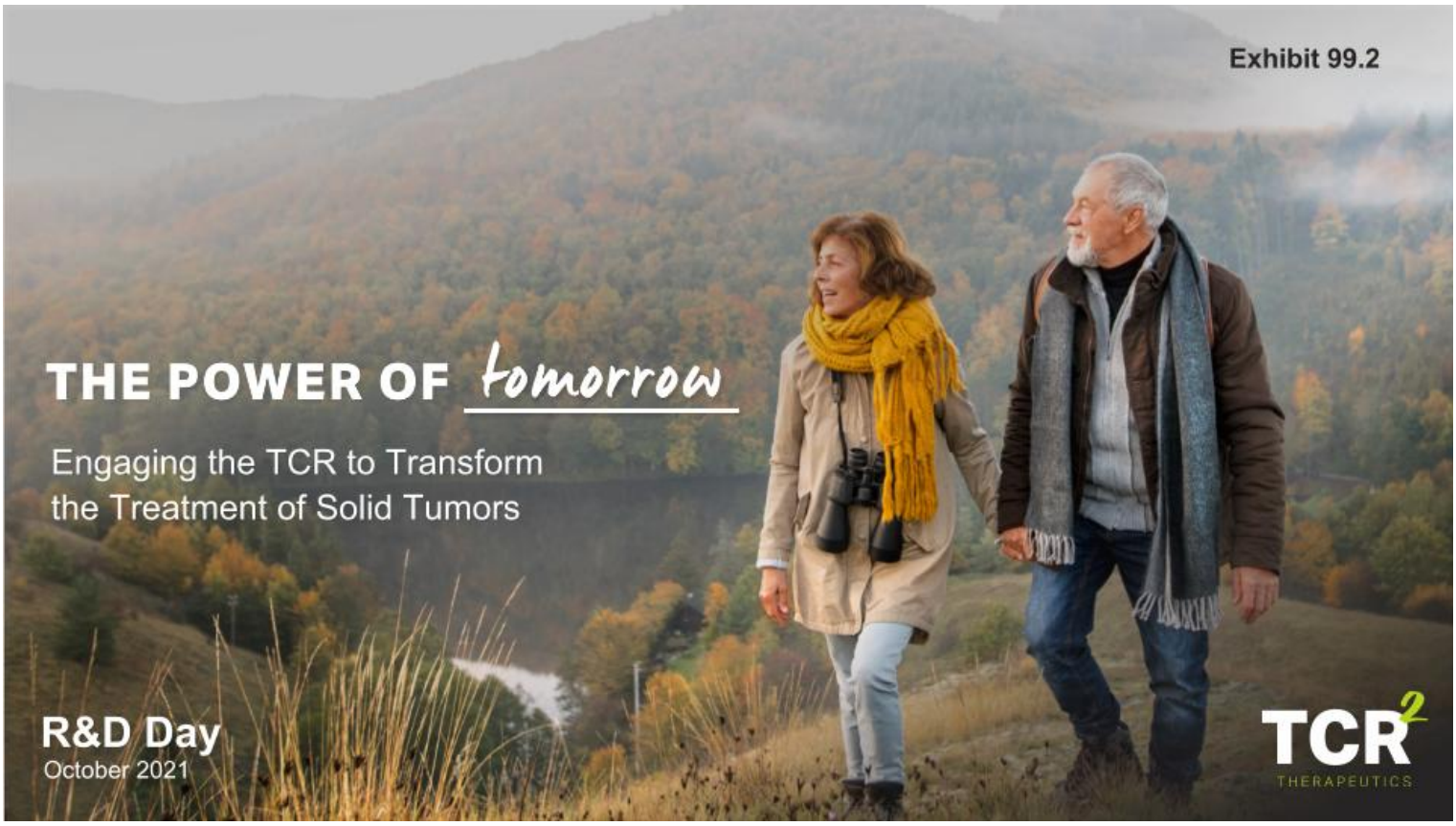
The expressed or implied forward-looking statements included in this press release are only predictions and are subject to a number of risks, uncertainties and assumptions, including, without limitation: uncertainties inherent in clinical studies and in the availability and timing of data from ongoing clinical studies; whether interim results from a clinical trial will be predictive of the final results of a trial; the possibility that positive results from preclinical studies and correlative studies may not necessarily be predictive of the results of TCR^2's planned clinical trials, including the Phase 1/2 clinical trial of gavo-cel; the risk that the results from the Phase 1/2 clinical trial of gavo-cel will not support further development and marketing approval; the risk that TCR^2 may be unable to gain approval of gavo-cel and its other product candidates on a timely basis, if at all; the risk that TCR^2 has over-estimated the potential patient population for its product candidates, if approved; the risk that the current COVID-19 pandemic will impact TCR^2's clinical trials and other operations; and other risks set forth under the caption "Risk Factors" in TCR^2's most recent Annual Report on Form 10-K, most recent Quarterly Report on Form 10-Q and its other filings with the Securities and Exchange Commission. In light of these risks, uncertainties and assumptions, the forward-looking events and circumstances discussed in this press release may not occur and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements. You should not rely upon forward-looking statements as predictions of future events. Although TCR^2 believes that the expectations reflected in the forward-looking statements are reasonable, it cannot guarantee that the future results, levels of activity, performance or events and circumstances reflected in the forward-looking statements will be achieved or occur.

Moreover, except as required by law, neither TCR^2 nor any other person assumes responsibility for the accuracy and completeness of the forward-looking statements included in this press release. Any forward-looking statement included in this press release speaks only as of the date on which it was made. We undertake no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law.

Investor and Media Contact:

Carl Mauch
Director, Investor Relations and Corporate Communications
TCR^2 Therapeutics Inc.
(617) 949-5667
carl.mauch@tcr2.com

Exhibit 99.2


THE POWER OF tomorrow
Engaging the TCR to Transform
the Treatment of Solid Tumors
R&D Day
October 2021
TCR2
THERAPEUTICS

Forward Looking Statements

This presentation has been prepared by TCR2 Therapeutics Inc. ("we," "us," or "our") and contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our development plans, our clinical results and other future conditions. All statements, other than statements of historical facts, contained in this presentation, including express or implied statements regarding our expectations for the Phase 1/2 clinical trials of gavo-cel and TC-110, our expectations for the safety and efficacy of our product candidates and enhancements, including gavo-cel and TC-110, compared to current T-cell therapy approaches, our expectations regarding the estimated patient populations and related market opportunities in gavo-cel's and TC-110's targeted indications, and our expectations regarding manufacturing of our product candidates are forward-looking statements. These statements are based on management's current expectations and beliefs and are forward-looking statements which involve risks and uncertainties that could cause actual results to differ materially from those discussed in such forward-looking statements.

Such risks and uncertainties include, among others: uncertainties inherent in clinical studies and in the availability and timing of data from ongoing clinical studies; whether interim results from a clinical trial will be predictive of the final results of a trial; the possibility that positive results from preclinical studies and correlative studies may not necessarily be predictive of the results of our planned clinical trials, including the Phase 1/2 clinical trials of gavo-cel and TC-110; the risk that the results from the Phase 1/2 clinical trials of gavo-cel and TC-110 will not support further development and marketing approval; the risk that we may be unable to gain approval of gavo-cel, TC-110 and our other product candidates on a timely basis, if at all; the risk that we have over-estimated the potential patient population for our product candidates, if approved; the risk that the current COVID-19 pandemic will impact our clinical trials and other operations; and the other risks set forth under the caption "Risk Factors" in our most recent Annual Report on Form 10-K for the year ended December 31, 2020, as filed with the SEC on March 16, 2021, as updated in our most recent Quarterly Report on Form 10-Q for the quarter ended June 30, 2021, as filed with the SEC on August 5, 2021, and in our future filings with the SEC available at the SEC's website at www.sec.gov. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. You should not place undue reliance on any forward‑looking statements, which speak only as of the date they are made.

While we may elect to update these forward-looking statements at some point in the future, we assume no obligation to update or revise any forward-looking statements except to the extent required by applicable law. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements.

Agenda

Leading the Way in Solid Tumors	**Garry Menzel**, President and CEO
Utilizing the Full Power of the TCR	**Robert Hofmeister**, CSO
Beginning with gavo-cel and Mesothelin • History of Anti-Mesothelin Clinical Therapies • Phase 1 Clinical Trial & Next Steps	**Raffit Hassan**, National Cancer Institute **Alfonso Quintás-Cardama**, CMO
Boosting TRuC-T Cells with Enhancements • TC-510: PD-1:CD28 Switch • IL-15 Enhancements	**Robert Hofmeister**, CSO **Robert Tighe**, VP of Research
Novel Targets: CD70	
Advancing our Allogeneic Program	**Robert Hofmeister**, CSO
Beyond Oncology with TRuC T-Regs	
Closing Remarks	**Garry Menzel**, President and CEO
Q&A	

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Leading the Way in Solid Tumors

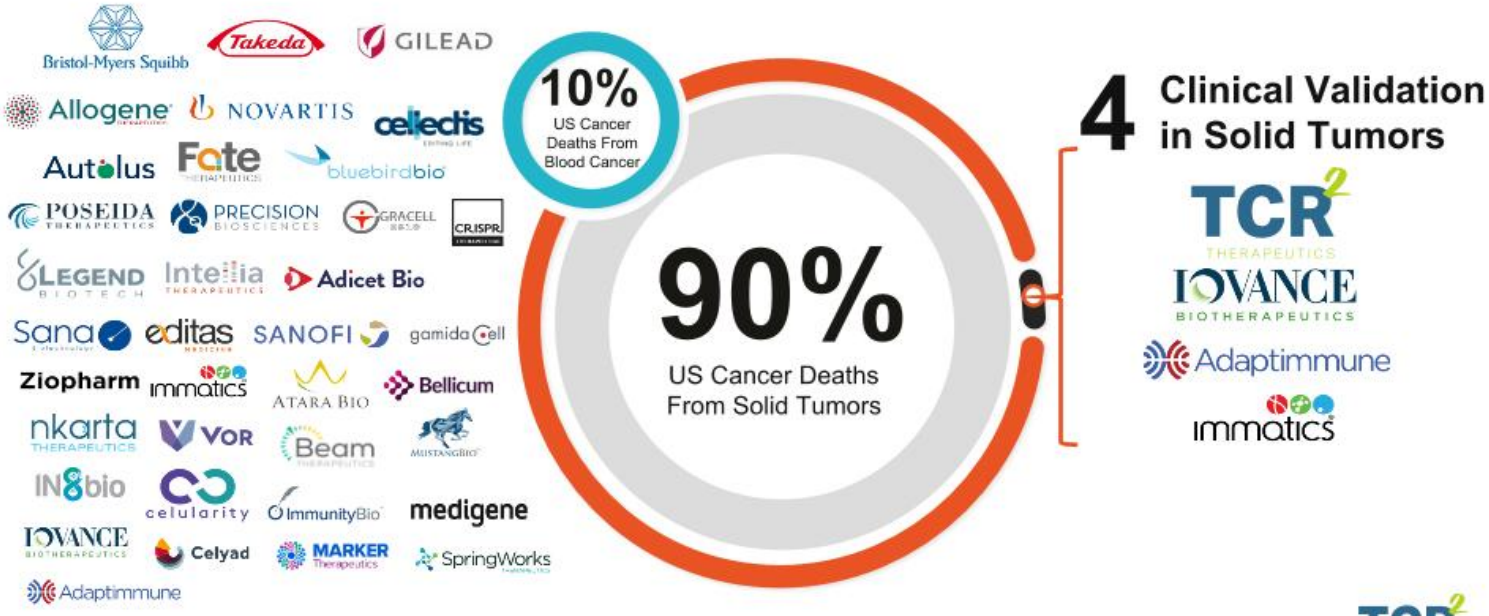
Garry Menzel, Ph.D.
President and Chief Executive Officer

TCR² THERAPEUTICS


A Focused Solid Tumor T Cell Therapy Company
We discover. We innovate.
We are redefining the TCR complex.
We are changing what it means to be diagnosed with solid tumors.
Our mission is to deliver the promise of tomorrow to patients.
TCR2
THERAPEUTICS

The Solid Tumor Market Is a Significant and Open Opportunity

Clinically Validated Cell Therapies in Solid Tumors All Utilize the Full TCR Complex



Ref: ACS Cancer Statistics 2020

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Advancing a Diverse Pipeline of Solid Tumor Programs

Target	Indication(s)	Program	Enhancement / Combo	Discovery	Lead Optimization	IND Enabling	Phase 1/2	Phase 2/3
Oncology								
Autologous								
MSLN	Ovarian cancer, NSCLC, MPM, Cholangiocarcinoma	gavo-cel						
MSLN	Ovarian cancer, NSCLC, MPM, Cholangiocarcinoma	gavo-cel	Checkpoint inhibitor					
MSLN	Solid tumors	TC-510	PD-1 switch					
CD70	Renal cell carcinoma	TC-520	IL-15					
GPC3	Solid tumors							
Nectin-4	Solid tumors							
Allogeneic								
MSLN	Solid tumors	gavo-cel	IL-15 / PD-1 switch					
CD70	Renal cell carcinoma	TC-520	IL-15 / PD-1 switch					
Autoimmune								
HLA-A*02	Solid organ transplant / GvHD							

MSLN, mesothelin; NSCLC, non-small cell lung cancer; MPM, mesothelioma; GvHD, Graft versus Host Disease

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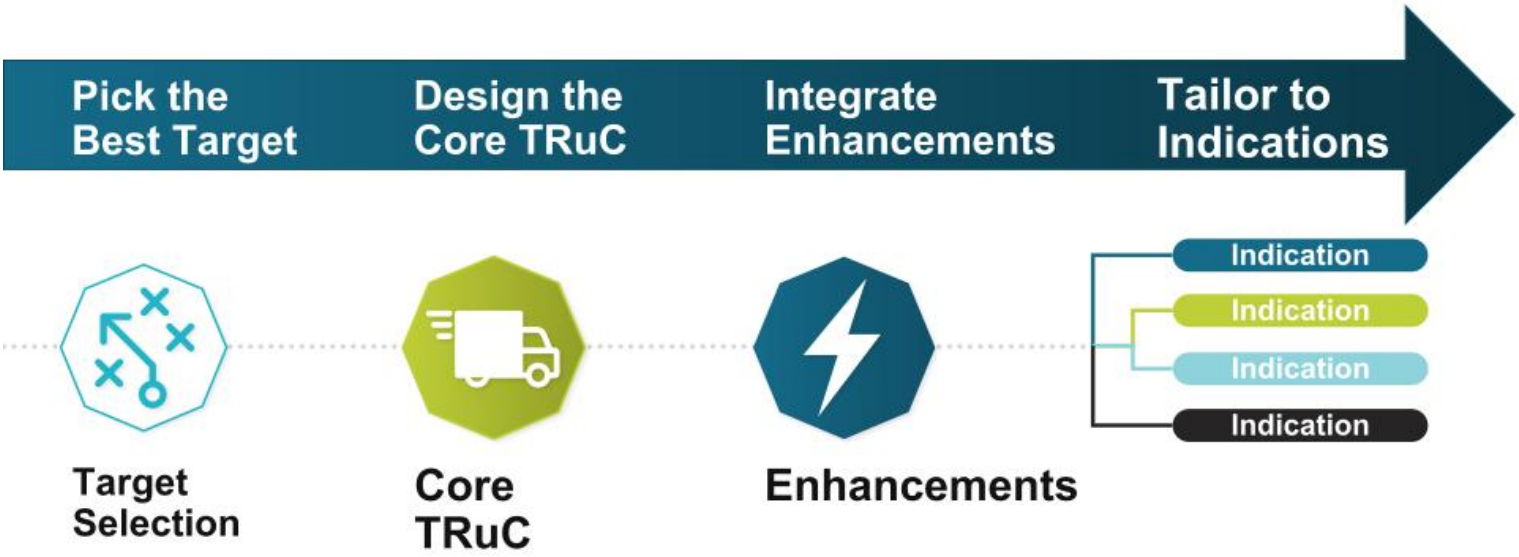
Executing Pipeline Value Strategy



Utilizing the Full Power of the TCR

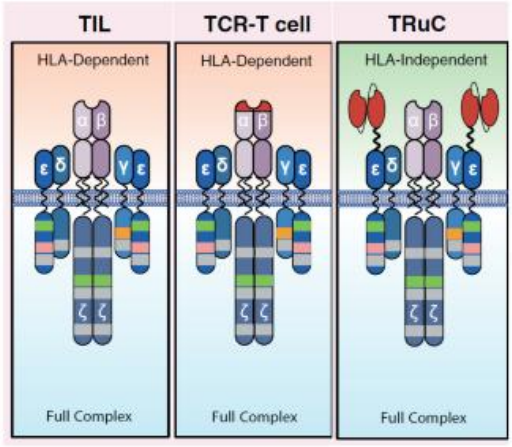
Advancing a Differentiated Approach in Cell Therapy

Robert Hofmeister, Ph.D.
Chief Scientific Officer

TCR² THERAPEUTICS

TCR-Based Therapies: An Innovative Approach in Solid Tumors

- **A Superior Starting Point**: utilization of the full TCR retains auxiliary molecules of TCR signal transduction pathway
  - Critical element limiting CAR activity in solid tumors
- **Success in Solid Tumors with Full TCR Complex**: encouraging clinical responses (CRs, PRs) in patients with solid tumors, even with refractory disease, emerging with TCR-based therapy studies (i.e. TILs, TCR-Ts and TRuCs)



Hardy et al., Immunotherapy 2020

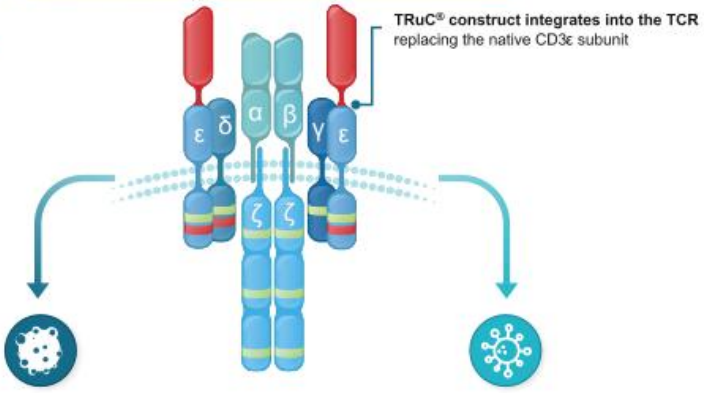
Evolving the Natural Power of the TCR

Advancing a New Cell Therapy Modality to Create Life-Transforming Medicines

Harnessing the TCR Complex

- Comprehensive T cell activation to **tackle solid tumors**
- **No HLA restriction** supports broad patient access
- **Versatile platform** with flexibility to add enhancements
- **Potential across oncology and autoimmune** in multiple high-value indications

TRuC® Platform
(T Cell Receptor Fusion Constructs)



Cytotoxic TRuC-T Cells
Solid Tumors
Hematological Malignancies

TRuC Treg Cells
Autoimmune Diseases
Transplant Rejection

Mesothelin Targeted Therapies

Raffit Hassan, M.D.
Chief of Thoracic and GI Malignancies Branch at the National Cancer Institute

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gavo-cel Clinical Update

Identification of RP2D within Reach

Alfonso Quintás-Cardama, M.D.
Chief Medical Officer

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Patients Treated post ESMO

Dose Level	DL3 ($1x10^8/m^2$)	DL3.5A ($3x10^8/m^2$ fractionated)		
Patients	18	19	20	21
Age/Sex	59/F	66/F	50/M	43/F
Diagnosis	MPM	MPM	MPM	MPM
MSLN 2+/3+	60	92	75	70
No. Prior Rx	5	9	7	10
ICI	No	Yes	Yes	Yes
Anti-MSLN Rx	No	No	Yes	No
Bridging Therapy	Yes	Yes	Yes	Yes
LD Chemo	Yes	Yes	Yes	Yes
Highest CRS	Gr 1	Gr 1	Gr 2	None yet

Data Cutoff – October 13, 2021

ICI, immune checkpoint inhibitor; MSLN, mesothelin; LD, lymphodepletion; CRS, cytokine release syndrome; Gr, grade; MPM, malignant pleural/peritoneal mesothelioma

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gavo-cel Phase 1 Summary and Next Steps

- MTD identified at DL5 ($5x10^8/m^2$ following LD)
  - Currently testing lower doses with fractionation
    - DL3.5A: 3/3 split patients treated
- Identification of RP2D before year-end

- Next steps:
  - *Proposed Phase 2 design to FDA, including:*
    - New mesothelin expression cutoff
    - gavo-cel redosing
    - Checkpoint combinations
  - *Initiation of Phase 2 study*

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gavo-cel + Checkpoint Inhibitor Combination Rationale

- Cancer limits antitumor responses by expressing immune checkpoints such as PD-L1[1,2,3]
- PD-L1 expression is induced by T cell–secreted IFN-γ and TNF-α[2]
- The addition of PD-(L)1 blockade therapy[1,2,3]:
  - Rescues the function of exhausted T cells
  - Enhances persistence and function of CAR T cells
  - Induces epitope spreading and neoantigen response through promotion of endogenous immunity
- Clinical synergism between anti-MSLN CAR T and pembrolizumab shown in mesothelioma[4]

[1]Cherkassky et al. J Clin Invest 2016; [2]Grosser et al. Cancer Cell 2019; [3]Adusumilli et al. Sci Transl Med 2014; [4]Adusumilli et al. Cancer Discov 2021

Boosting TRuC-T Cells with Enhancements

Matching Enhancements with Indication Specific Biology

Robert Hofmeister, Ph.D.
Chief Scientific Officer

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The TRuC Platform Has Exponential Options

Solid Tumor Franchise

MSLN, CD70, GPC3, NECTIN4

Enhancements

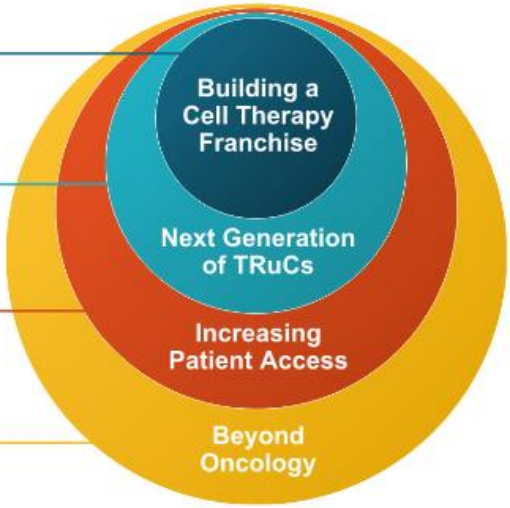
PD-1 Switch, IL-15 and Many More

Allogeneic Platform

POC for Lead Candidate, αβ and γδ chain TRuCs

TRuC-Tregs

Multiple High-Value Indications – GvHD, T1D, ALS, MS

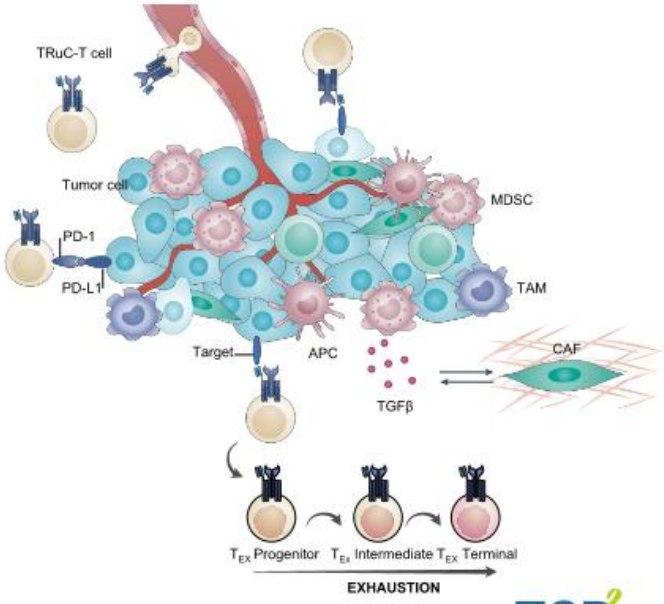


MSLN, mesothelin; POC, proof-of-concept; GvHD, Graft versus Host Disease; T1D, Type 1 Diabetes; ALS, amyotrophic lateral sclerosis; MS, multiple sclerosis

Immunosuppressive Mechanisms in Solid Tumors Drive T Cells into a Dysfunctional State

With our enhancements we want to solve for the major hurdles of cell therapy

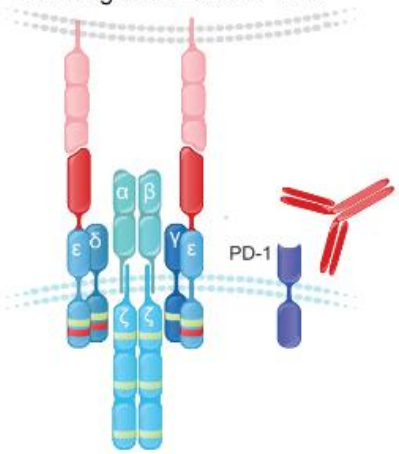
- Inhibition of T cell activity by immunosuppressive factors (PD-1, TGFβ)
- Chronic T cell stimulation resulting in T cell exhaustion
- Lack of stemness limiting durability of response



Enhancements Endow TRuC-T Cells with Characteristics to Improve Efficacy in Solid Tumors

gavo-cel + anti-PD1

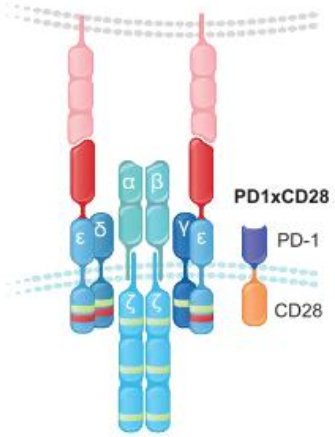
Re-invigorate TRuC-T cells



- Enhances gavo-cel and TILs in the tumor microenvironment
- Reverts T cell exhaustion

PD1xCD28 Switch

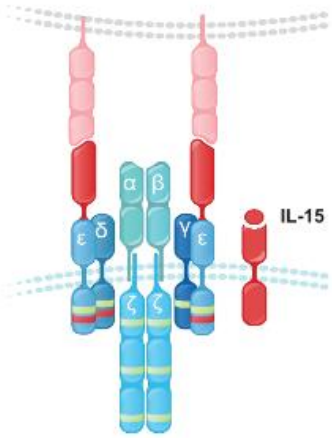
Maintenance of T cell potency



- Enhances T cell activity in tumor microenvironment (TME)
- Delays T cell exhaustion

IL-15

Stem-like properties for persistence



- Maintains naïve and memory T cell phenotype
- Enhanced survival, proliferation and T cell fitness

PD1xCD28 & IL-15 Are Suited for Different Tumor Environments

PD1xCD28 Switch

- Provides an extra boost (PD-L1 dependent co-stimulation) by increasing effector function
- Longer persistence of TRuC-T cells leads to tumor regression in rechallenge model
- Co-stimulation may protect TRuC-T cells from activation induced cell death (AICD) tumors with low antigen expression

Tumors with high PD-L1 expression and established role of the PD-1 pathway

IL-15

- Provides an autonomous survival signal in the absence of TCR signal
- Endows TRuC-T cells with stem-like properties (upregulation of TCF1)
- Very strong proliferation upon TCR activation, preferential effect on CD8+ T cells
- Long persistence of cells post tumor clearance

Tumors with low antigen expression and less relevance of PD-1 pathway

TCR2 THERAPEUTICS

TC-510: gavo-cel + PD1xCD28 Switch

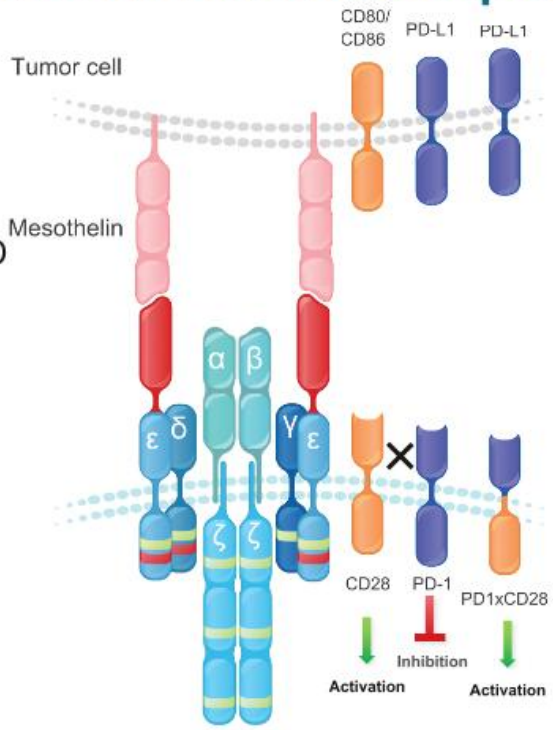
Expanding our Reach into Mesothelin-Expressing Tumors

Robert Tighe
Vice President of Research

TCR2 THERAPEUTICS

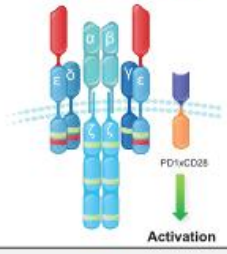
Enhancing gavo-cel with a PD1xCD28 Switch Receptor

- TC-510 is designed to improve upon the already promising clinical activity observed with gavo-cel
- PD1xCD28 switch is designed to hijack the PD-1/PD-L1 inhibitory pathway, transforming it into a potent costimulatory signal
- Preclinically, TC-510 shows enhanced T cell function and anti-tumor activity compared to gavo-cel

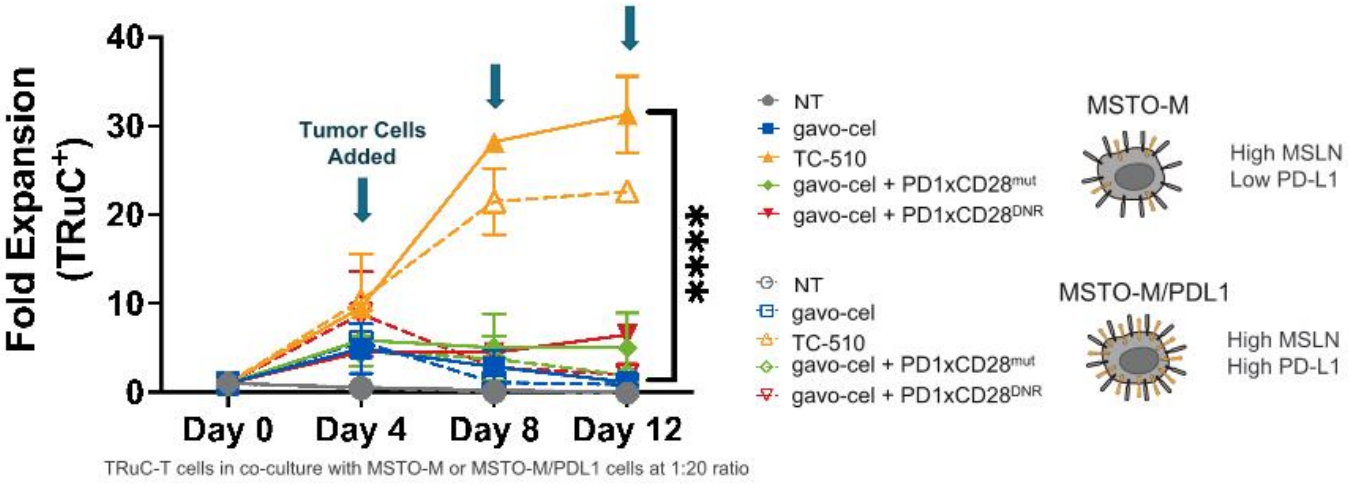


Elucidating TC-510's Mechanism of Action

Costimulatory Signaling vs. PD-1 Dominant Negative Receptor (DNR)

	gavo-cel	TC-510 gavo-cel + PD1xCD28	gavo-cel + PD1xCD28^{Mut}	gavo-cel + PD1 DNR
				
TRuC Signaling	**Yes**	**Yes**	**Yes**	**Yes**
Co-Receptor	**No**	**Active Signaling and Decoy Function**	**Decoy Function**	**Decoy Function**

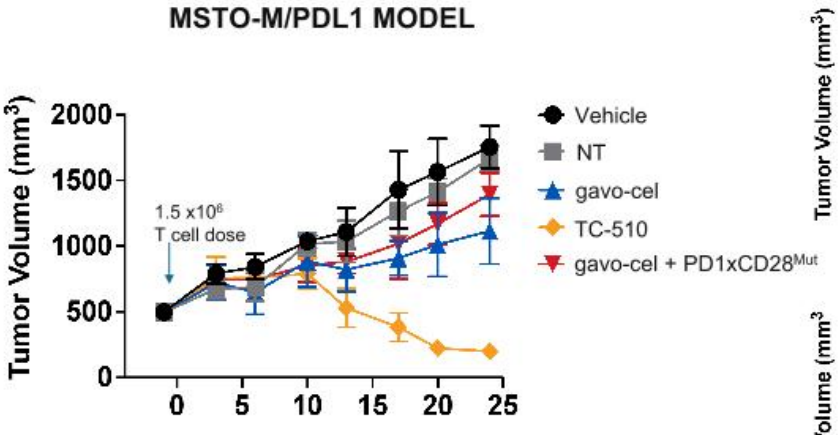
TC-510 Demonstrates Improved *In Vitro* Expansion and Persistence vs gavo-cel

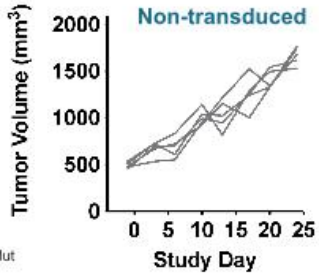


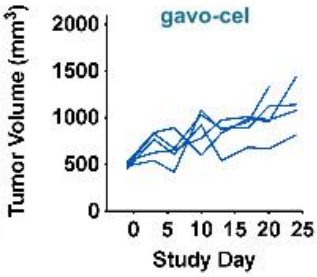
TRuC-T cells in co-culture with MSTO-M or MSTO-M/PDL1 cells at 1:20 ratio

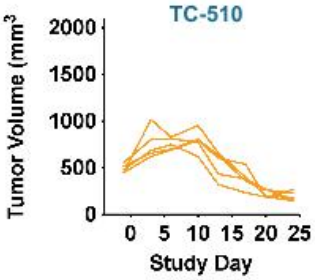
- Increased expansion and persistence was observed against both high and low PD-L1 tumor targets
- Enhancement of expansion is primarily driven by signaling activity rather than decoy function

Against Tumors with High PD-L1 Expression, TC-510 Shows Superior Efficacy to gavo-cel *In Vivo*









TC-510: Opportunities for an Enhanced gavo-cel

- Preclinical data demonstrated:
  - Enhances efficacy of gavo-cel against PD-L1 overexpressing tumors
  - Prevented exhaustion upon repeated antigen stimulation
- Further expand the TRuC platform into additional solid tumor indications
- Promising strategy to improve the clinical efficacy of TRuC-T cells
- IND-enabling studies ongoing with filing expected in 1Q 2022

TCR2 THERAPEUTICS

IL-15 Enhancements

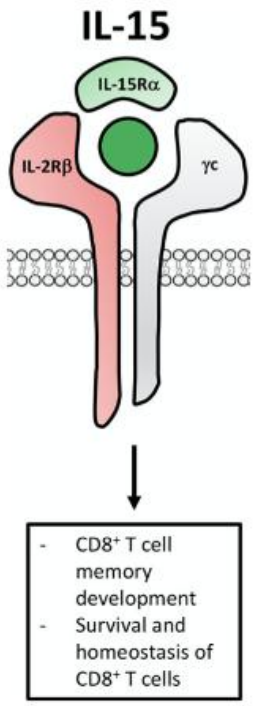
Evolving TRuC-T Cell Persistence and Phenotype with IL-15

Robert Tighe
Vice President of Research

TCR2 THERAPEUTICS

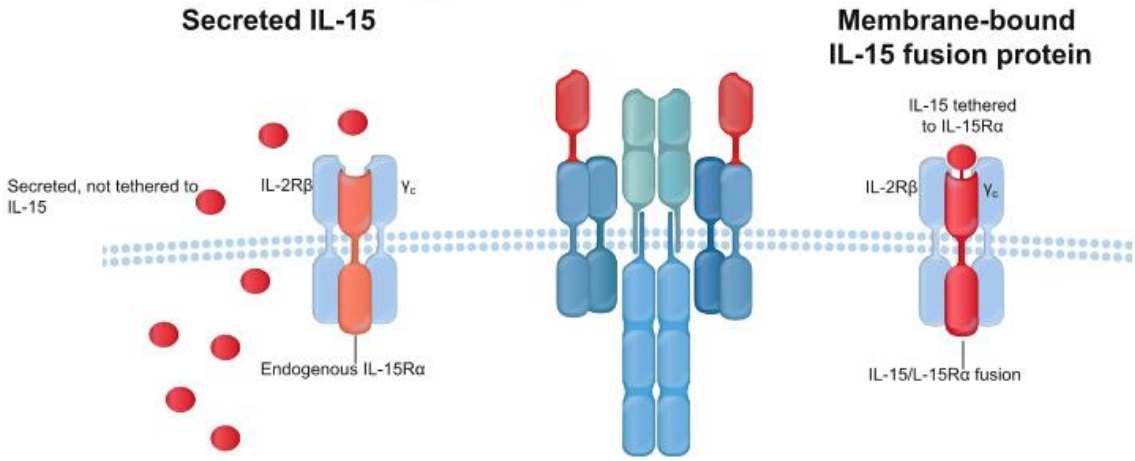
IL-15 as an Enhancement for T Cell Function

- γ chain cytokine important for the development and homeostasis of NK cells and CD8+ T cells
- IL-15 has a crucial role in the maintenance and survival of naïve and central memory T cells with high proliferative capacity
  - Promotes the survival and proliferation of naïve and central memory CD8+ T cells
  - Promotes survival of T cells in the absence of TCR stimulation
- Inhibits IL-2 activation induced cell death (AICD)
- Based on these properties, IL-15 signaling is expected to enhance TRuC-T cell persistence and improve efficacy against solid tumors



Dwyer et. al. *Frontiers in Immunology* 2019.

Head-to-Head Testing of Two IL-15 Concepts that Primarily Differ in Modes of Signaling



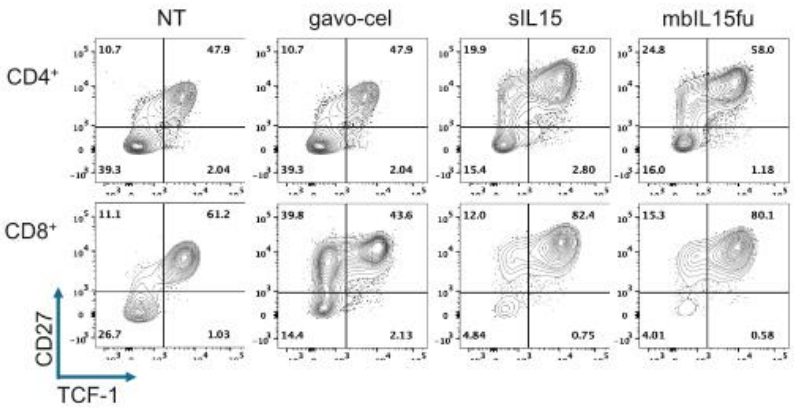
- Constitutively secreted, soluble form that binds to endogenous IL-15Rα
- IL-15 presentation to IL2Rβ/γc in *cis* and *trans*

- Constitutively overexpressed IL-15/IL-15Ra fusion
- IL-15 presentation to IL2Rβ/γc in *cis* and *trans*

TCR2 THERAPEUTICS

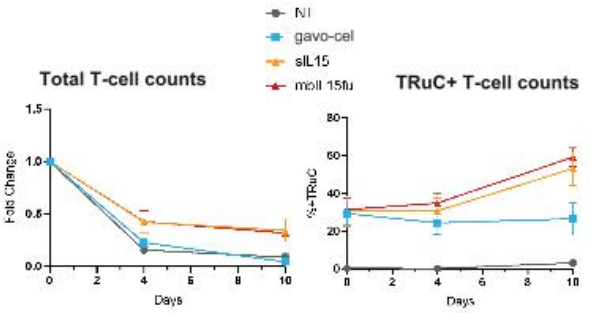
IL-15 Expressing TRuC-T Cells Upregulate Stemness Markers and Show Autonomous Persistence *In Vitro*

Upregulation of Stemness Markers Following T Cell Activation



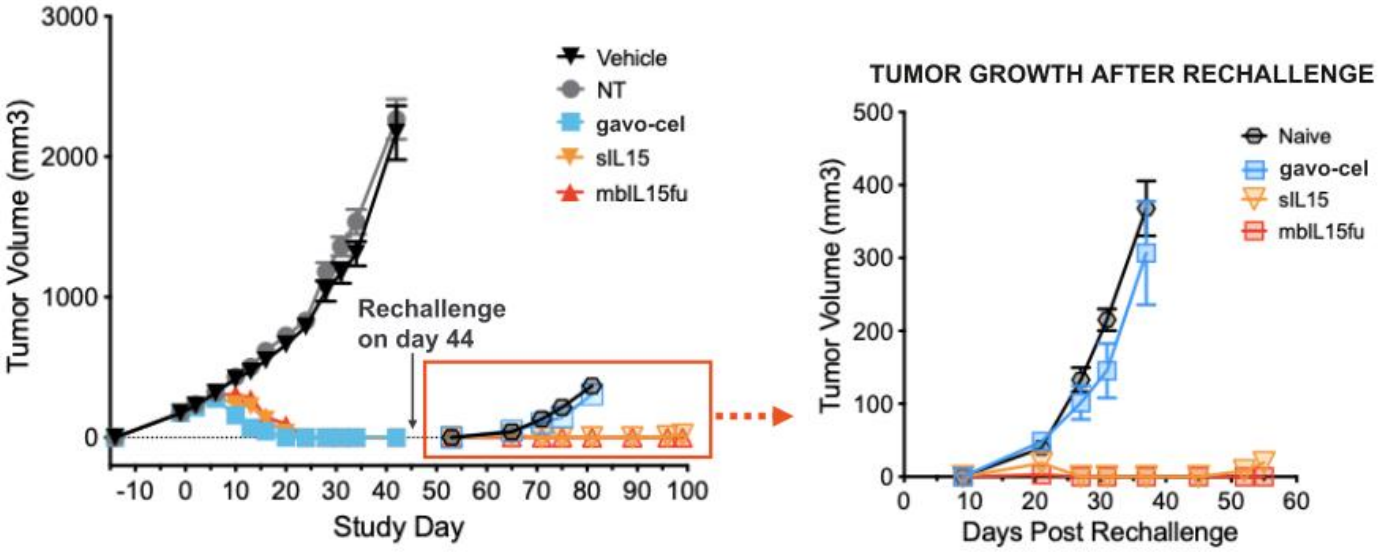
T-cells were cocultured with MSTO-MSLN cells for 96 hours and then stained for TCF-1 and CD27 and analyzed by flow cytometry.

Enhanced Persistence in Absence of Stimulation



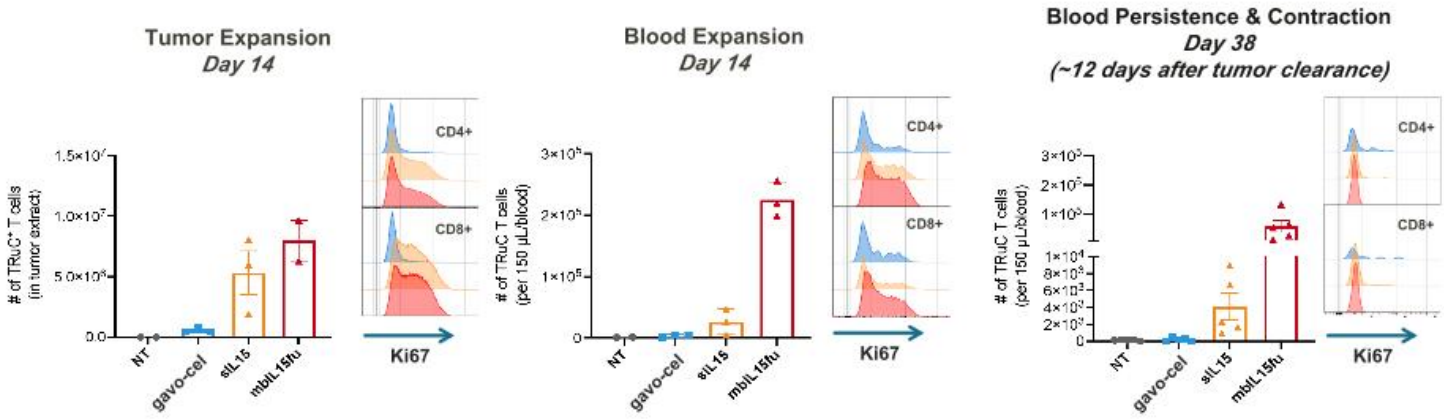
T-cells were cultured in vitro for 10 days in cytokine-free media and cell numbers were quantified on indicated days

IL-15 Enhanced TRuCs Show Durable Functional Persistence *In Vivo* that Protects from Tumor Rechallenge



TCR2 THERAPEUTICS

IL-15 Enhanced TRuC-T Cells Increased Proliferation & Persistence with Contraction after Tumor Clearance



- IL-15 enhanced TRuC-T cells show significantly increased expansion in tumor and blood
- Higher expansion and proliferation of mbIL-15fu vs. sIL-15
- After tumor clearance, IL-15 enhanced T cells stop proliferating and start to contract

Early Data Supports Role of IL-15 in Phenotype and Persistence

- Preclinical data demonstrated:
  - Favorable phenotype with CD8+ naïve/T cell central memory cells
  - Enhanced stemness markers associated with long-term proliferative capacity
  - Increased persistence in the absence of external, activating stimuli
  - Increased expansion and persistence to fully protect from tumor rechallenge
- Enabled to potentially increase TRuC-T cell persistence in cancer patients for improved efficacy against solid tumors

TCR² THERAPEUTICS

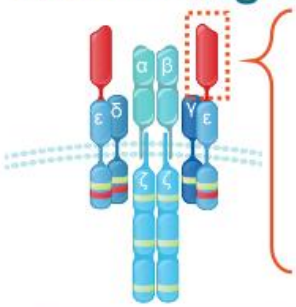
Identification of Novel Targets

CD70, GPC3, NECTIN4

Robert Tighe
Vice President of Research

TCR2 THERAPEUTICS

Novel Target Selection Process



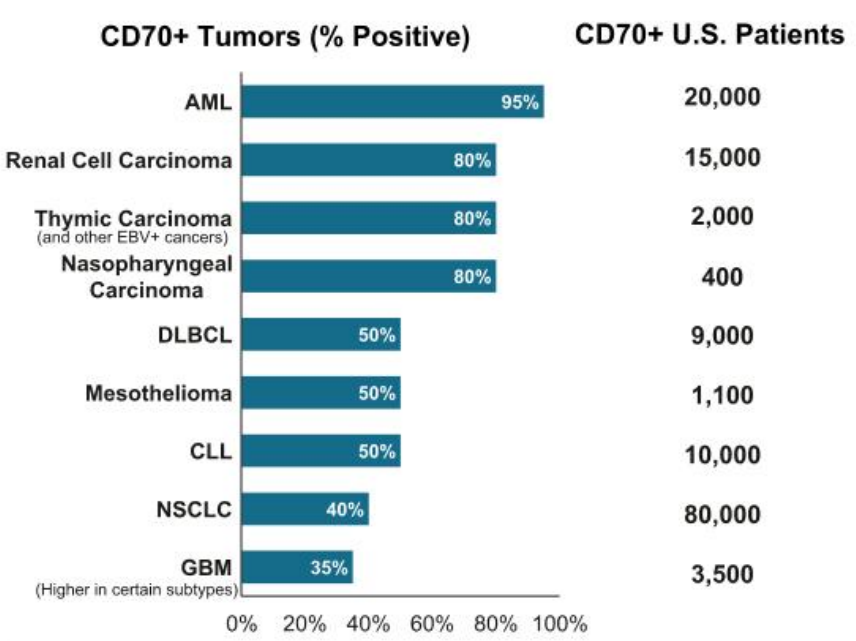
1. **Expression profile** of the tumor antigen
2. **Scientific evidence and validation** of the tumor antigen
3. **Evaluation of target indication** patient population, market landscape and competition
4. **Clinical path forward**

Target	Characteristics	Indications
CD70	• Increases frequency and activation of Tregs in TME • Limited expression to highly activated T cells and B cells, epithelial cells of the thymic medulla	• Wide range of solid tumors, hematological malignancies
GPC3	• Linked to proliferation and oncogenic pathways, Wnt, Yap and hedgehog • Proteolytically shed domain is detected in serum • Little expression in adult healthy tissue, associated with poor prognosis	• Liver cancer
NECTIN4	• Role as stimulatory co-receptor for prolactin receptor • Soluble form detected in serum, prognostic risk factor • Abundant in fetal tissue but declines in adult life, overexpressed in many cancers (~97% of urothelial cancers)	• Urothelial cancer

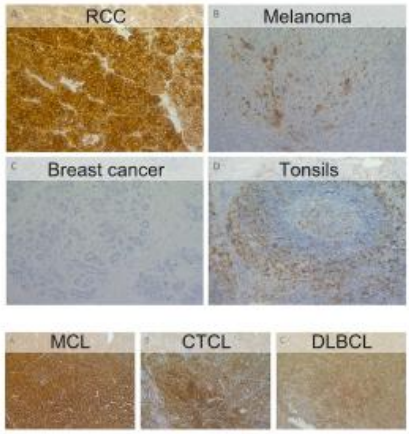
TCR² THERAPEUTICS

CD70 Population is Large and Spans a Diverse Set of Tumors

Up to 141,000 CD70+ patients in the US alone



Examples of Tissue Staining

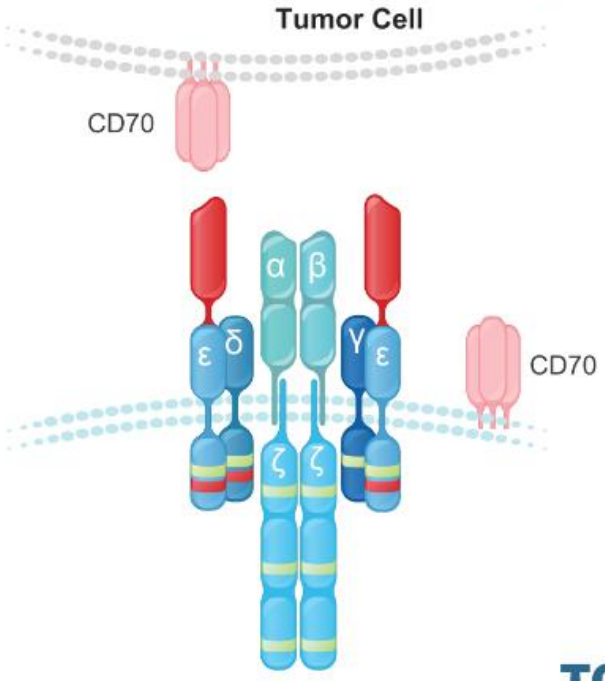


Flieswasser et al., Cancers 2019

Sources: SEER, Flieswasser et al., Cancers 2019, Agathanggelou et al., Am J Pathol. 1995, Riether J Exp Med 2017

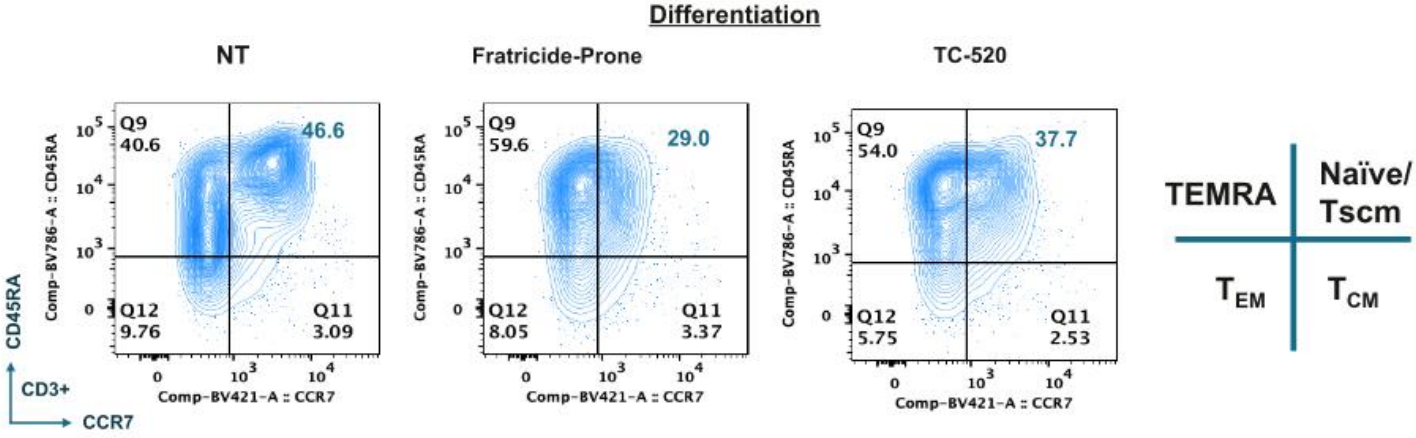
CD70: Highly Attractive Target with an Innate Fratricide Challenge

- Expressed in a broad range of solid and hematological malignancies
- Expression in normal, healthy cells limited to activated lymphocytes (i.e., subset of T cells, B cells, and dendritic cells)
- Expression in activated T cells renders CD70-directed T cell therapies susceptible to fratricide



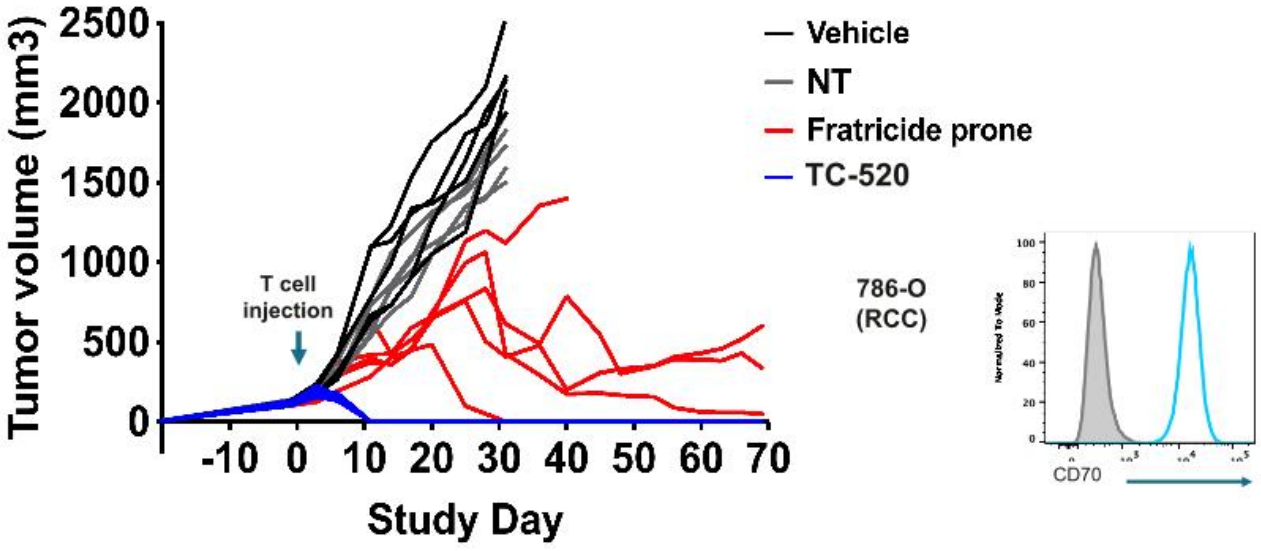
Discovery of Fratricide-Resistant CD70 Lead (TC-520)

Characterization at end of 10-day manufacturing process



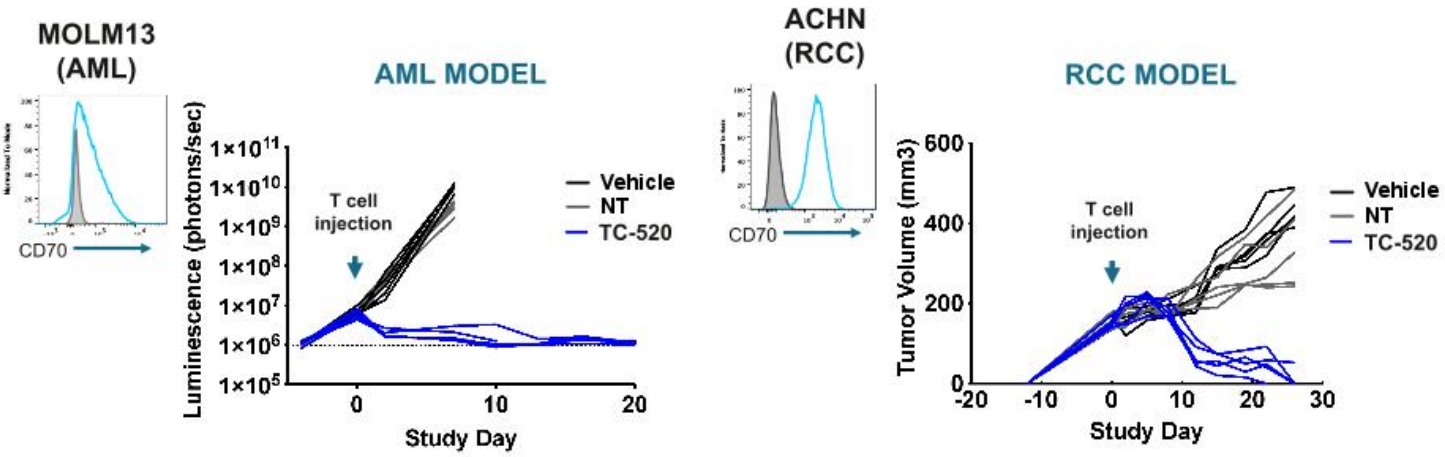
- Fratricide-resistant TC-520 shows a more robust naïve/T_{SCM} phenotype important for *in vivo* efficacy/persistence
- TC-520 further shows normal expansion and lower basal activation
- TC-520 shows high *in vitro* potency against tumor targets with low levels of CD70 expression

TC-520 Exhibits Potent and Persistent *In Vivo* Efficacy



RCC, renal cell carcinoma

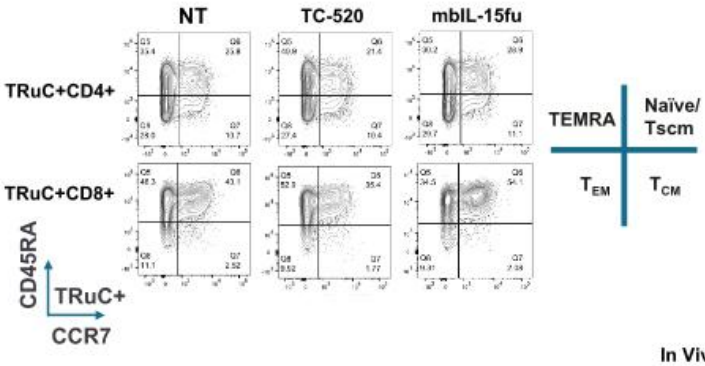
TC-520 Exhibits Potent Efficacy in Tumor Models with Low and Moderate Expression

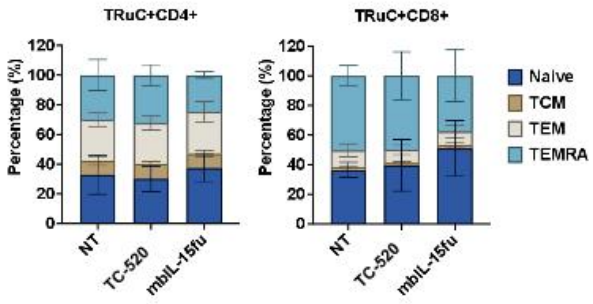


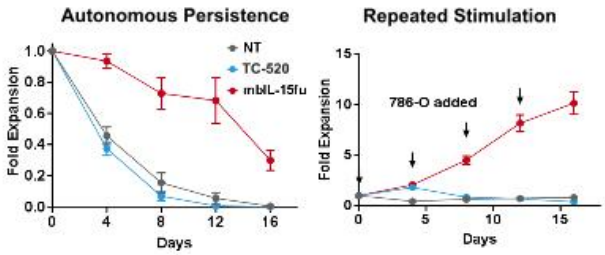
- A single dose of TC-520 induced tumor regression in a disseminated AML model with low CD70 expression and a RCC model with moderate CD70 expression.

AML, acute myeloid leukemia; RCC, renal cell carcinoma

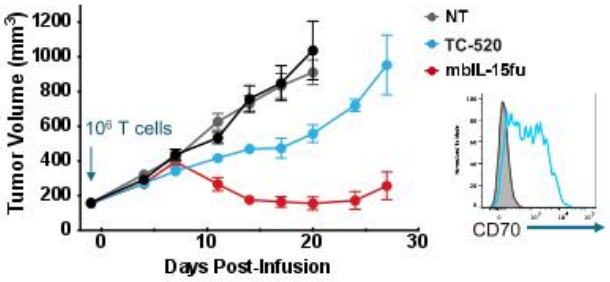
IL-15 Enhancement Improves TC-520 Phenotype and Function







In Vivo Efficacy at Suboptimal Dose in CD70 low H1975 NSCLC model



TC-520: Pursuing Path Forward with Enhancements

- Preclinical data demonstrated:
  - Successfully identified fratricide-resistant anti-CD70 TRuC that displays a favorable phenotype
  - Potent *in vivo* efficacy against tumors with low, moderate and high CD70 expression
- Potential to target new indications (both solid tumors and hematological malignancies), broadening the market opportunity of TRuC-T cells
- IL-15 enhancement further improves the phenotype and preclinical efficacy of TC-520
- IND-enabling studies for TC-520, our TRuC-T cell targeting CD70 co-expressing an IL-15 enhancement, targeted in 2022 with an indication focus on renal cell carcinoma

TCR2 THERAPEUTICS

Allogeneic TRuCs

Broadening Platform, Increasing Patient Access

Robert Hofmeister, Ph.D.
Chief Scientific Officer

TCR² THERAPEUTICS

Expanding TRuC-T Cell Reach with Allogeneic Capabilities

Potency

- Use of healthy donor apheresis product
- Engineering of primary T cells to maintain functional and phenotypical properties of T cells
- Restoration of the full TCR for optimal T cell activation

Safety

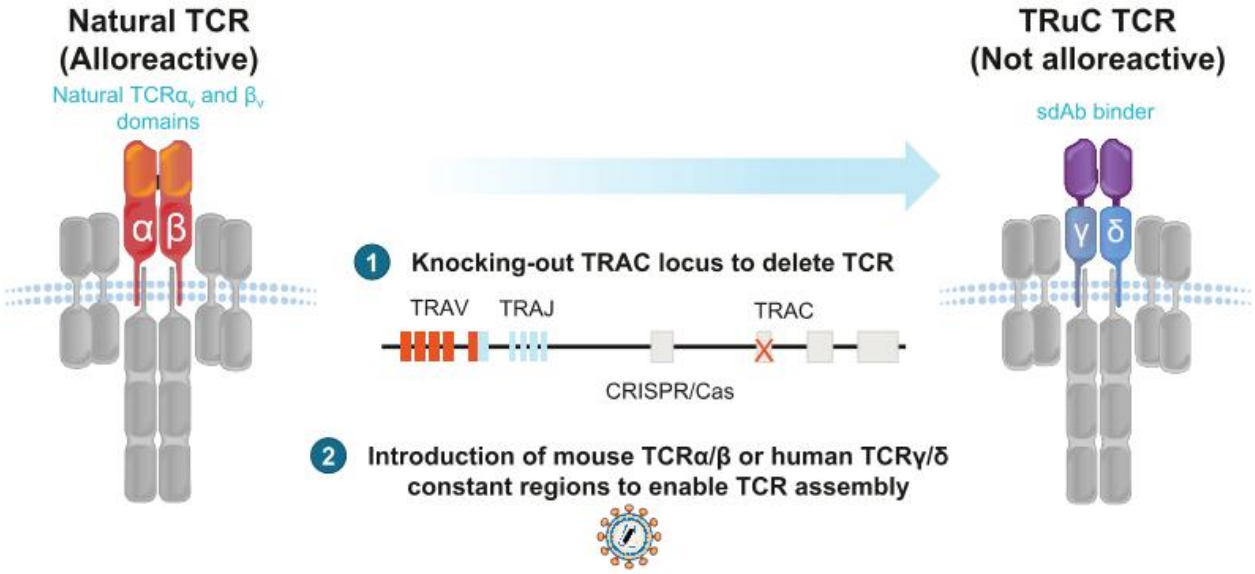
- Removal of TCR variable domains to avoid GvHD
- Introduction of fully human TCRγ/δ constant domains to reduce risk of immunogenicity

Persistence

- Knock-out of B2M to avoid host rejections
- Co-expression of IL-15 to increase T cell fitness and persistence

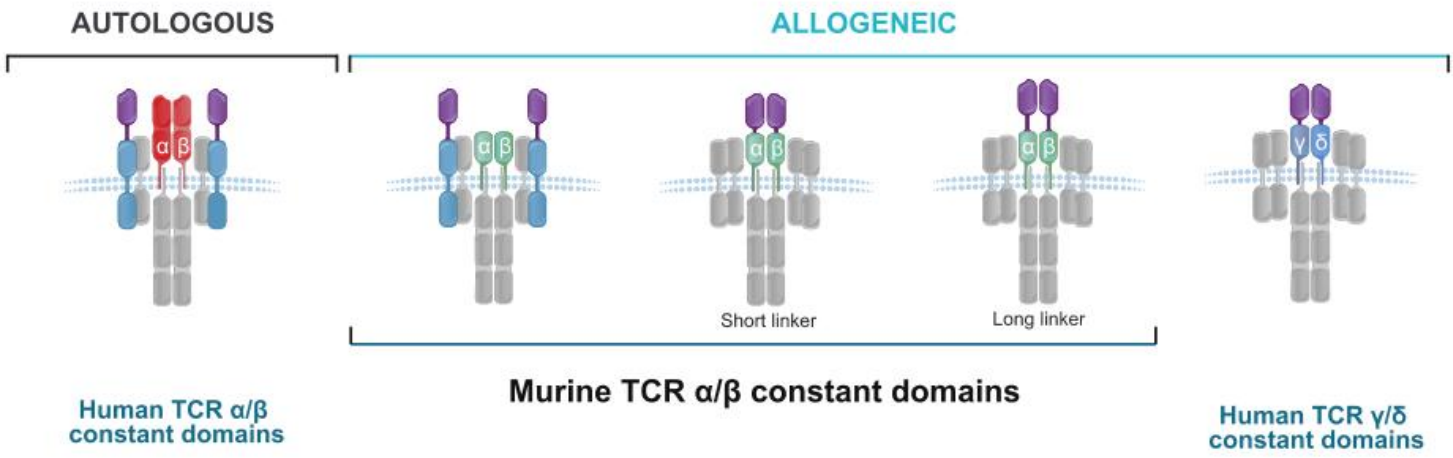
TCR² THERAPEUTICS

Allo TRuC-T Cells are Generated in a Two-Step Process



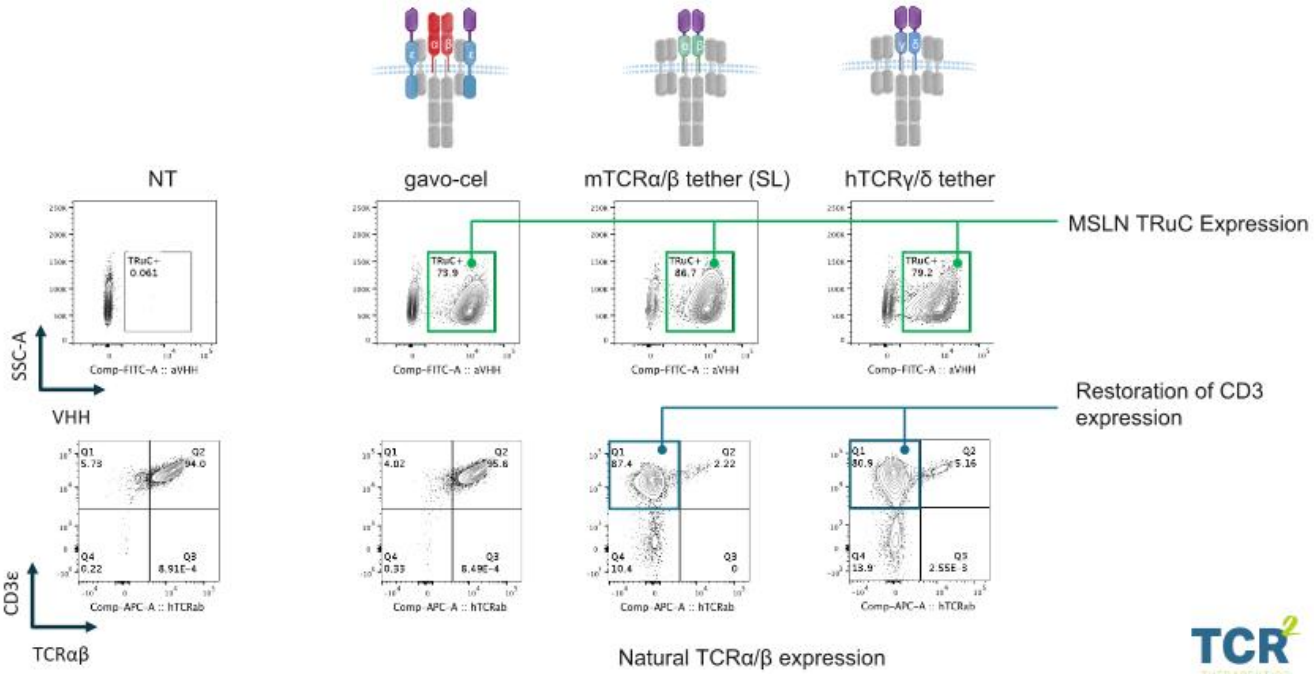
TCR2 THERAPEUTICS

Optimization and Selection of Allo TRuC Designs



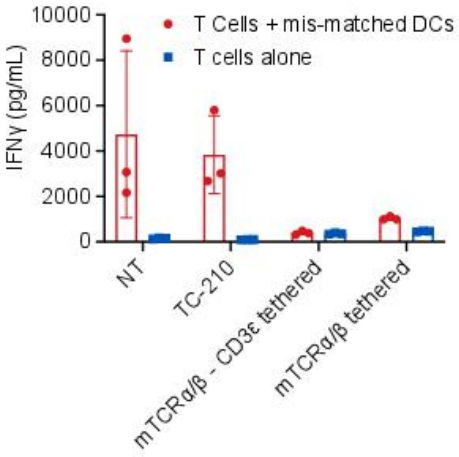
- The re-expression of murine TCR α/β or γ/δ constant domains avoids mis-pairing with the endogenous human TCRβ subunit thereby enhancing the restoration of the TCR

Re-Introduction of TCR Constant Domains Restores TCR Expression on Allo TRuC-T Cells

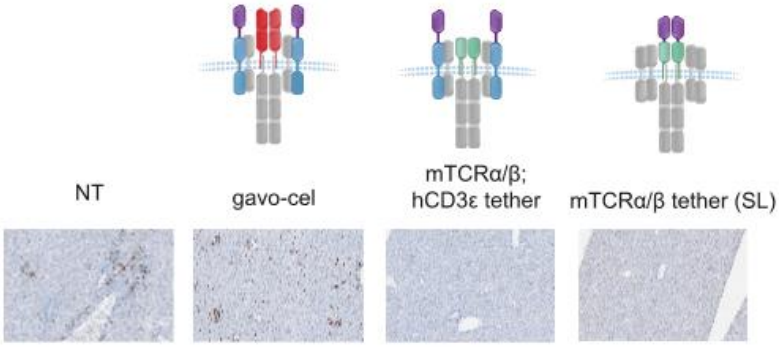


Mesothelin-Specific Allo TRuC-T Cells Do Not Cause GvHD

Mixed Lymphocyte Reaction



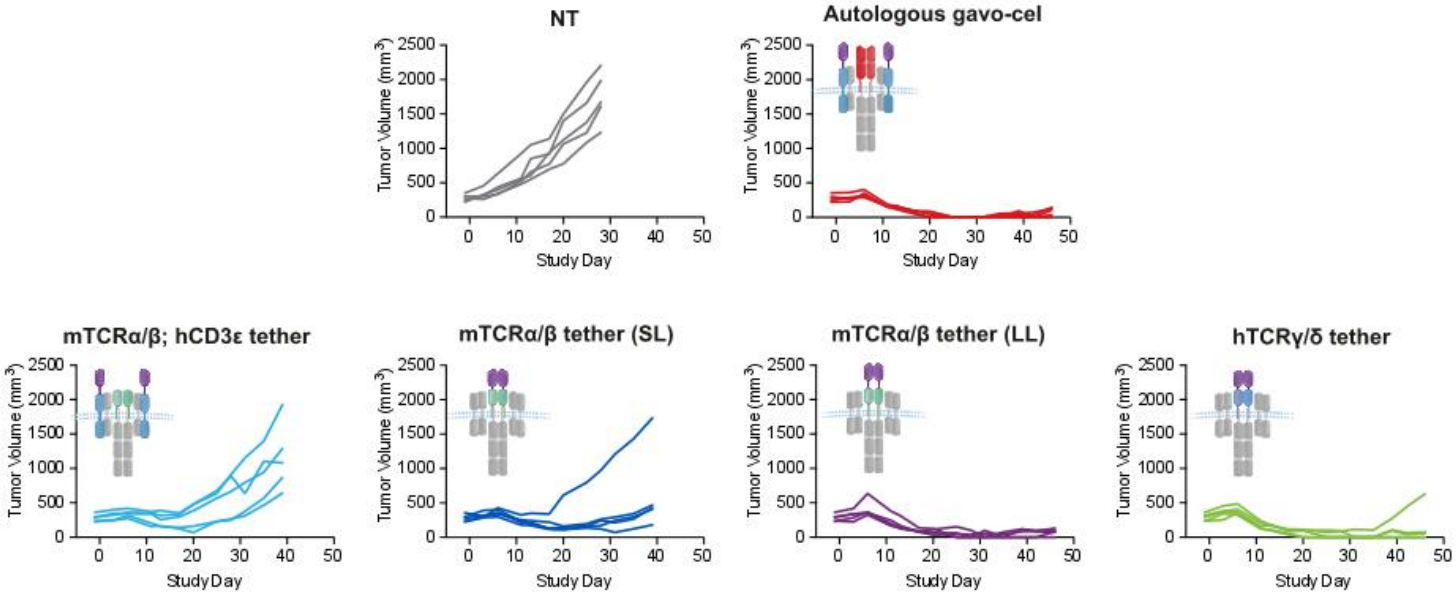
Immunohistochemistry



No infiltration of CD7⁺ human T in the livers 50 days post non-transduced (NT) or TRuC-T cell administration

TCR² THERAPEUTICS

Equivalent Anti-Tumor Activity of gavo-cel with Allogeneic TRuC-T Cells



Allogeneic Platform Further Expands Patient Reach

- Preclinical data demonstrated:
  - TCR complex can be restored in TRAC-deficient T cells and efficiently integrated enabling full TCR signaling
  - Allogeneic TRuCs show equivalent efficacy to autologous TRuCs
  - Allogeneic TRuCs are not alloreactive and do not cause GvHD in mice
- Currently evaluating the combination of enhancements with allogeneic TRuC-T cells to improve persistence and stemness
- Identification of lead candidate in 2022
  - Lead based on fully human TCR γδ fusion constructs to reduce the risk of immunogenicity
  - Knock-out B2M in addition to TRAC to mitigate host rejection

TCR² THERAPEUTICS

TRuC Tregs

Diversification Opportunity in Autoimmune Diseases

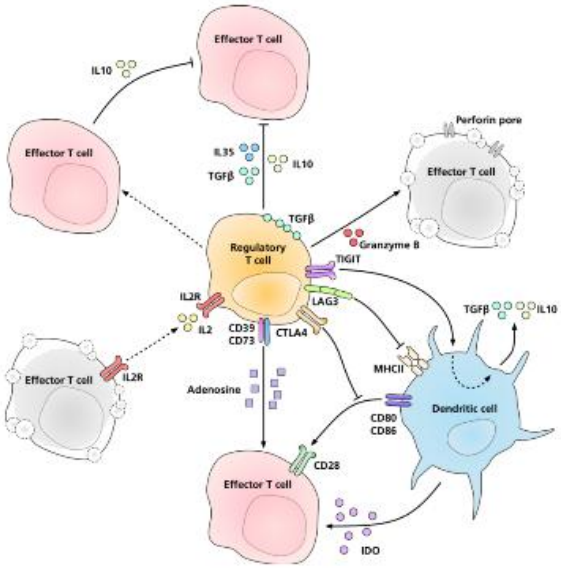
Robert Hofmeister, Ph.D.
Chief Scientific Officer

TCR² THERAPEUTICS

Innovative T Cell Engineering for the Treatment of Autoimmune Diseases

Regulatory T Cells are the Master Controllers of Self-Tolerance

- Secretion of immunosuppressive cytokines
- Direct killing of effector T cells and APCs
- Delivery of co-inhibitory signals
- Secretion of immunosuppressive metabolites
- Deprivation of growth factors by acting as an IL-2 sink



Adapted from Vignali DAA. et al., (2008) Nature Immunology 8(7)525-532

TCR² THERAPEUTICS

TRuC Tregs at Forefront of Autoimmune Cell Therapy

Adoptive Treg Therapy has Evolved and Gained Significant Momentum

Increasing specificity and potency

Polyclonal Tregs

- >100 patients worth of feasibility and safety data with no GVHD or "class-switching" to T_{eff} cells
- Early signs of efficacy in GVHD[1,2] and transplant[3]
- Tregs detected up to 1-year post-infusion[4]

Antigen Specific Tregs

- Antigen reactive Tregs selected and expanded
- Efficacy seen in preclinical models where polyclonal Tregs fail[5]
- Early signs of efficacy demonstrated in liver transplant[6] and Crohn's[7]

Engineered Tregs

- Engineered to stabilize phenotype and enhance homing
- First CAR-Treg clinical trial in 2021, targeting HLA-A*02 in organ transplant[8]
- Preclinical data suggest tissue-specific antigen is sufficient for Treg function[9]

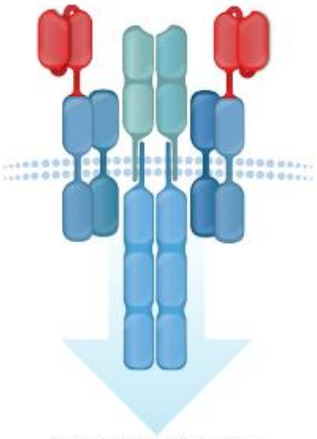
~$670M Raised by <10 Early-Stage Private Treg-focused Biotechs in 2021

1. Tronkowski, 2009, 2. Brunstein 2010, 3. Sawitzki, 2020, 4. Bluestone, 2015, 5. Stephens, 2009, 6. Todo, 2016, 7. Desreumaux, 2012, 8.Sangamo, 2021 9. Eshhar, 2014

TCR² THERAPEUTICS

TRuC Treg Function Predicated on the Natural TCR Signal

- **TCR Signal**
  - All TCR subunits (not just CD3ζ) have been shown to be important for Treg development and stability
    (Rudensky, 2016)
  - Residual inflammatory cytokine production reported when a CAR-Treg is activated via its CAR but not its TCR
    (Boroughs, 2019)
  - Certain costimulatory domains and contexts can drive CAR-Tregs to effector function
    (Dawson 2020)
- **Tissue Homing**
  - Like TRuCs targeting solid tumors, Treg efficacy is dependent on controlled and faster trafficking to tissues
- **T Cell Persistence**
  - CAR tonic signaling can cause a hyporesponsive, exhausted phenotype and decreased persistence (Lemarche, 2020)



Entire TCR Signaling

TRuC Tregs Can Address Multiple Therapeutic Markets

Neuroinflammatory Disorders

ALS, Myasthenia Gravis, Progressive Multiple Sclerosis

- Decreased Treg levels and Treg dysfunction are associated with several neurological diseases
- Opportunity to slow disease progression and delay disability in diseases with high need

Severe Autoimmune Disorders

Aplastic Anemia, Systemic Sclerosis

- Tregs can reduce pathogenic inflammation and restore homeostasis
- Opportunity to provide disease modifying therapies in high need indications

Transplant

Solid organ transplant, GVHD

- Tregs can drive tolerance to alloantigen rejection
- Opportunity to reduce or eliminate need for long -term immune suppression (and associated side effects)

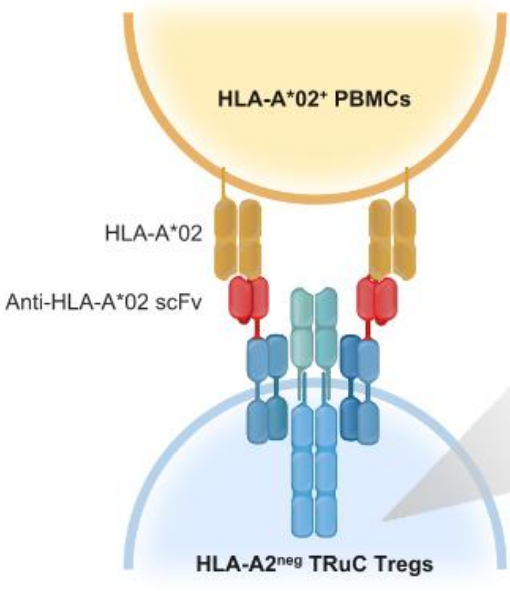
Large Autoimmune Markets

Type 1 Diabetes, Crohn's, Lupus Nephritis

- Large markets where even a small share of patients would be meaningful
- Opportunity to target refractory/ severe niches, possibility to drive long-term remissions or cures with single dose

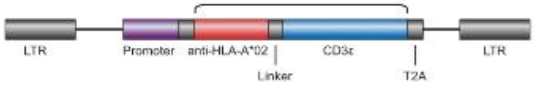
TCR² THERAPEUTICS

We Chose a GvHD Model to Demonstrate Proof-of-Concept



We tested the effect of Foxp3 overexpression on the TRuC Treg phenotype and functional activity

Construct 1: anti-HLA-A*02 TRuC

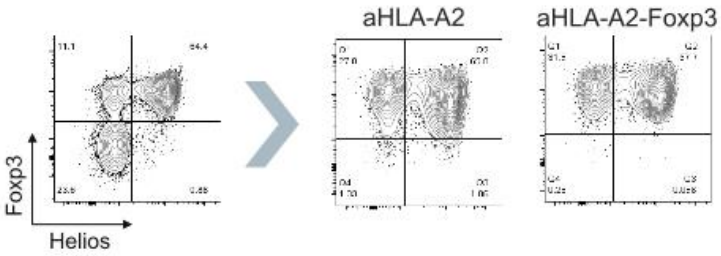


Construct 2: anti-HLA-A*02 TRuC + FOXP3

TRuC Treg Cell Product Maintains Treg Hallmarks: Foxp3 and Helios Expression and Hypomethylated TSDR/CNS

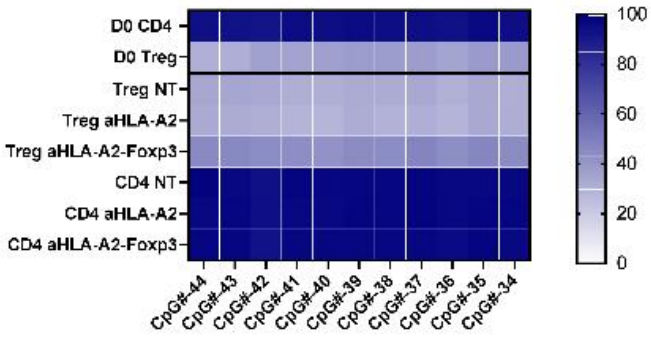
T_{REG} STARTING MATERIAL

TRuC T_{REG} PRODUCT



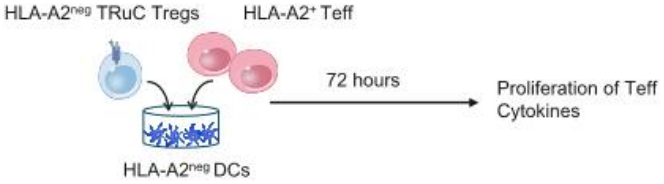
Anti-HLA-A*02 TRuC Treg cells maintain high expression of Foxp3 and Helios.

TSDR/CNS2 METHYLATION PHENOTYPE

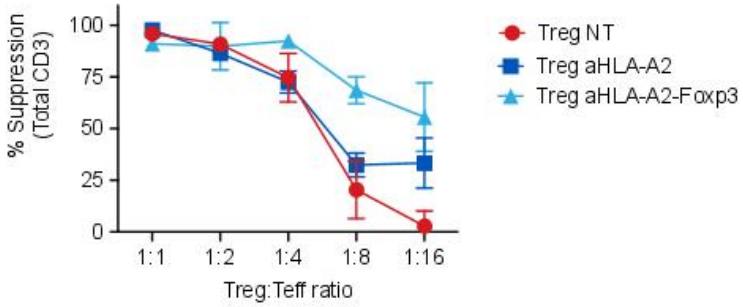


TRuC Treg cells maintain hypomethylated TSDR/CNS regions

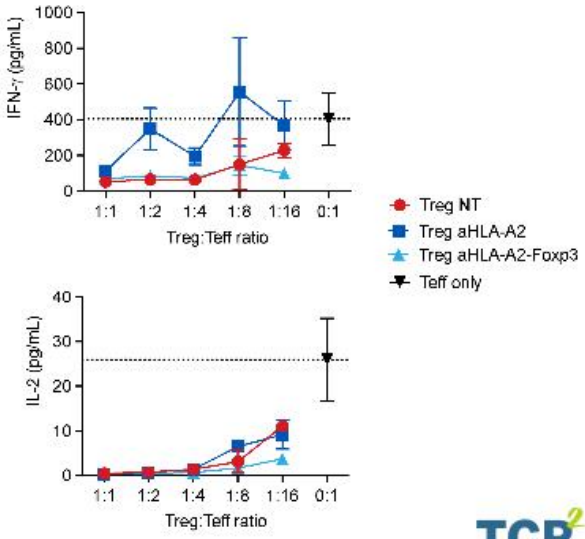
TRuC Treg Cells Suppress Effector T Cell Proliferation and Cytokine Secretion in an *In Vitro* MLR Assay



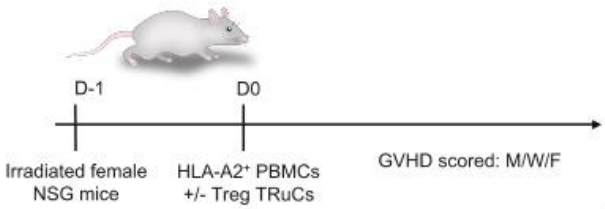
Inhibition of T cell proliferation

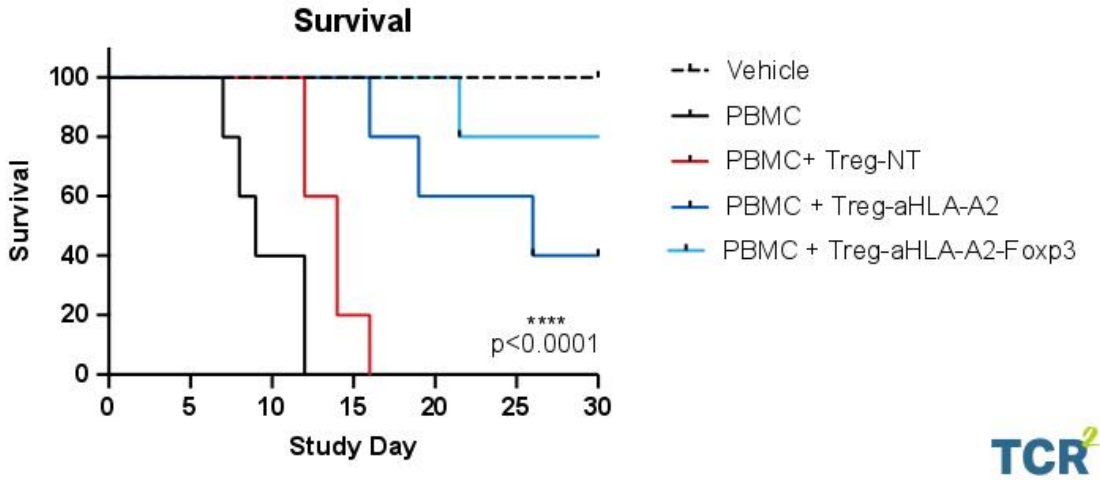


Inhibition of Cytokine Secretion



HLA-A*02-specific TRuC Treg Cells Provide Better Protection From GvHD than Polyclonal Treg Cells

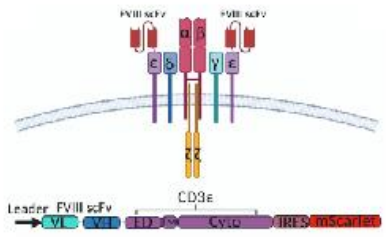




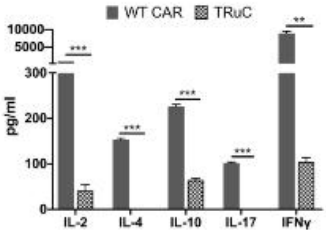
Potential of TRuC Treg Cells Independently Observed in a Mouse Hemophilia A Model

- CAR- or TRuC Tregs were generated against Factor VIII to prevent anti-Factor VIII formation
- CAR-Tregs secrete high levels of effector cytokines when stimulated *in vitro*
- TRuC Tregs suppressed the production of FVIII antibodies better than polyclonal Tregs at 4 and 8 weeks

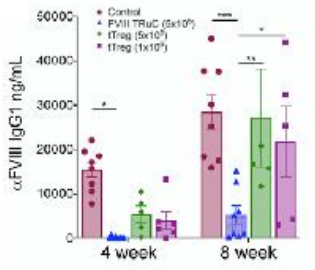
Construct Design



48-hr stimulation with recombinant FVIII



In vivo efficacy



Rana et al., Mol Therapy, 2021

A Significant BD Opportunity to Unlock TRuC Treg Platform Value

Represents Opportunity Outside of Oncology Focus

- TRuC Tregs build on our clinically validated TRuC-T cell cancer platform
  - Full TCR signaling important for Treg function
  - Natural signaling complex in Tregs to avoid overactivation and effector-like function
  - Established TRuC Treg IP with T cell engineering, PD and manufacturing in place
- Proof of Concept achieved
  - Robust process leading to 70-80-fold Treg expansion while sustaining Treg stability
  - TRuC Tregs targeting HLA-A*02 suppress effector T cells in MLR reaction
  - *In vivo* proof-of-principle for prevention of GvHD by HLA-A*02 PBMCs in a NSG model
- With investment in emerging Treg cell therapies increasing, the TRuC Treg platform is well positioned for leadership in autoimmune disorders
  - Differentiated TRuC Tregs could fill substantial unmet need, including larger indications

TCR² THERAPEUTICS

Closing Remarks

Garry Menzel, Ph.D.
President and Chief Executive Officer

Advancing a Diverse Pipeline of Solid Tumor Programs

Target	Indication(s)	Program	Enhancement / Combo	Discovery	Lead Optimization	IND Enabling	Phase 1/2	Phase 2/3
Oncology								
Autologous								
MSLN	Ovarian cancer, NSCLC, MPM, Cholangiocarcinoma	gavo-cel						
MSLN	Ovarian cancer, NSCLC, MPM, Cholangiocarcinoma	gavo-cel	Checkpoint inhibitor					
MSLN	Solid tumors	TC-510	PD-1 switch					
CD70	Renal cell carcinoma	TC-520	IL-15					
GPC3	Solid tumors							
Nectin-4	Solid tumors							
Allogeneic								
MSLN	Solid tumors	gavo-cel	IL-15 / PD-1 switch					
CD70	Renal cell carcinoma	TC-520	IL-15 / PD-1 switch					
Autoimmune								
HLA-A*02	Solid organ transplant / GvHD							

MSLN, mesothelin; NSCLC, non-small cell lung cancer; MPM, mesothelioma; GvHD, Graft versus Host Disease

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Q&A

TCR² Management and Dr. Hassan